REMARKS

Claim 39 has been amended by introducing the limitations of claim 40 to avoid an interpretation of claim 39 which was not intended. As the Office recognizes, the mutation that is introduced must extend beyond a single cell in order to be meaningful. In other words, the laboratory non-human mammal must be transgenic for the mutation. This limitation has now been introduced into claim 39, thus claim 40 has been canceled. As this limitation already appeared in claim 40, the amendment does not constitute new matter and entry of the amendment is respectfully requested.

Only new rejections have been proposed and these are addressed as follows:

Claim 37 was rejected as assertedly obvious over Contag (U.S. 5,650,138) in view of Okabe, *et al.* (*FEBS Letters* (1997) 407:313-319).

As to Contag, the Office asserts that the use of an E-selection promoter coupled to luciferase to evaluate drugs that affect inflammation is tantamount to screening for a modulator of the expression of a gene. Technically, this is correct; however, the claim is focused on gene regulation, not evaluating agents to treat particular reactions.

More importantly, as the Office kindly recognizes, Contag by itself does not suggest the invention. Contag does not suggest using techniques that involve mobile non-restrained animals despite the reference to an image that can be constructed in a short time scale relative to the time scale at which the un-immobilized subject moves. As taught by Contag at the bottom of column 15 at lines 55, *et seq.*, an important aspect of what they describe is a photodetector device with a high enough sensitivity to enable imaging of faint light from within a mammal in a reasonable amount of

time "preferably less than about 30 minutes." This time frame clearly cannot relate to a short time scale relative to the time scale at which the un-immobilized subject moves.

This is confirmed by the following text, extending through column 19 at line 40 which reveals that Contag is not even "observing" the presence, absence or intensity of fluorescence but rather counting photons in a complex manner. Office recognizes that the claimed invention includes much more straightforward methods of observation, such as simply viewing the animal under ultraviolet light in real time.

Contag also teaches away from the claim limitation that the fluorescent protein is autofluorescent. At column 9, beginning at line 65, Contag discourages the use of such labels because light is necessary to excite the fluorescence which, as Contag points out, interferes with the readout from the fluorescence self. For several paragraphs, continuing to line 27 in column 9, Contag points out all of the disadvantages of autofluorescent molecules. In subsequent paragraphs beginning at line 28, the Contag document discourages the use of fluorescence proteins as compared to small fluorescent molecules.

Taken as a whole, Contag describes a method of observation that in general requires restraint of the subject while imaging is done, requires an elaborate photon counting system as opposed to simple observation with the naked eye, and introduces additional complexities since not only is the enzyme, luciferase, needed but also expression systems for its substrate, luciferin (see column 10, lines 33-47). Contag also discourages use of the most commonly used fluorescent protein, green fluorescent protein in column 8, lines 42-45, by suggesting that longer wavelengths are favored.

While perhaps not recognizing the full extent to which Contag teaches away from the present invention, the Office does understand that Contag alone does not render the invention

obvious and this is greatly appreciated. Contag is therefore combined with Okabe who teaches, according to the Office, transgenic mice expressing green fluorescent protein. But the combination of Okabe with Contag actually teaches away from the invention. Okabe teaches production of green fluorescent protein under control of a chicken β actin promoter and a cytomegalovirus enhancer resulting in all of the tissues, with the exception of erythrocytes and hair, being green in response to ultraviolet light. Combining Okabe with Contag, then, would not permit the localization of gene expression as required by the claims, since the GFP is ubiquitously expressed. Therefore, this combination does not result in or suggest the claimed invention.

Claim 39 was rejected as assertedly obvious over Lin (U.S. 6,380,458) in view of Contag and Okabe. There appears to be some confusion as to which interpretation of claim 39 is to be considered in eliciting a rejection for non-enablement and which interpretation elicits one for obviousness. Applicants believe that the Examiner is correct that directly mutating the subject would not result in a transgenic mammal that could be evaluated for gene expression generally. However, it is that aspect that appears to be the subject of the rejection over the art rather than the rejection for non-enablement. Indeed, Lin clearly employs transgenic forms. So does Okabe. Applicants therefore assume that this rejection applies to instances where the mammal is transgenic.

Claim 39 is comparable to claim 37, except that instead of externally administered agent directly modulating gene function, a mutation is introduced to attain this result. Lin is cited as teaching genetically modified zebra fish that express green fluorescent protein. As the Office correctly states, Lin uses the reporter protein, for example, GFP, coupled to expression sequences for a gene to be evaluated, to determine the effect of a mutation on the expression of that gene.

That method is fine for zebra fish, which are transparent. It leaves the problem of real-time whole body fluorescence observations in animals that are not transparent, specifically mammals, to be solved by the present inventors.

This solution is not provided by combining Lin with Contag and Okabe for the same reasons set forth above. As noted, Contag teaches away from using fluorescent protein as a label for imaging mammals and Okabe specifically prevents noting the locations of the expression of the gene as required by the claims.

The teachings of Lin of using an expression system for a fluorescent protein to assess the effect of an independent mutation is acknowledged, but the further combination with Contag and Okabe does not suggest the invention for the foregoing reasons.

Claims 39 and 40 were rejected as assertedly non-enabled. As noted above, the description of this rejection on page 12 appears to relate to instances other than those reflected in the combination of claims 39 and 40, and thus it appears that this rejection is moot.

Conclusion

The combination of Contag the Okabe cannot suggest the invention with or without the presence of Lin, since Contag teaches only methods that are applicable to restrained non-mobile subjects and teaches away from the use of fluorescent protein and Okabe suggests a method to label all tissues of an organism with green fluorescent protein which would obviate any determination of additional gene expression by virtue of this marker. The rejection of claims 39 and 40 for lack of enablement appears to be moot since the rationale for that rejection is no longer reflected in the claims.

For these reasons, claims 37 and 39 are in a position for allowance and passage of these claims to issue is respectfully requested.

If minor issues remain that could be resolved by phone, a telephone call to the undersigned would be greatly appreciated.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762002710.

Respectfully submitted,

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